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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)
	10/564,994	BEEBE ET AL.
	Examiner WU-CHENG Winston SHEN	Art Unit 1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If no period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) Responsive to communication(s) filed on 07/09/2010.
- 2a) This action is **FINAL**. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 1-133 is/are pending in the application.
 - 4a) Of the above claim(s) 1-66, 78-80, 85-88 and 94-133 is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 67-77, 81-84 and 89-93 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on 18 January 2006 is/are: a) accepted or b) objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
 - a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) Notice of References Cited (PTO-892)
- 2) Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date 08/31/2010
- 4) Interview Summary (PTO-413)
Paper No(s)/Mail Date: _____
- 5) Notice of Informal Patent Application
- 6) Other: _____

DETAILED ACTION

Claim amendments filed on 03/08/2010, which include claim amendments filed on 11/24/2009, have been entered. The IDS filed on 08/31/2010 have been considered.

This application is 10/564,994 a 371 of PCT/US04/23078 07/19/2004 which claims benefit of provisional application 60/487,932 filed on 07/18/2003, and claims benefit of provisional application 60/499,921 filed on 09/04/2003, and claims benefit of provisional application 60/526,585 12/04/2003.

Election/Restrictions

In response to the office action mailed on 06/09/2010 regarding requirement of election of species between claim 67 and claim 133 (a new claim filed on 03/08/2010), Applicant's election with traverse of claim 67 in the reply filed on 07/09/2010 is acknowledged. The traversal is on the ground(s) that the examination of claims 67 and 133 together would not pose a serious burden on the Examiner, and a search of the prior art of claim 67 would also necessarily encompass a search of the prior art for claim 133. This is not found persuasive because, as stated in the restriction mailed on 06/09/2010, claims 67 and 133 recite two distinct circuit configurations designed for distinct sequential pulses with specified durations and amplitudes generated by the first circuit and by the second circuit. It is further noted that search burden is not germane to PCT lack of unity practice.

Claims 1-133 are pending. Claims 67, 81, and 89 are amended.

Claims 1-66, 78-80, 85-88, and 94-133 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 67-77, 81-84, and 89-93 are currently under examination

The requirement is still deemed proper and is therefore made FINAL.

Claim Rejection - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

1. Previous rejection of claims 67-77, 81-84, and 89-93 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention, is **withdrawn** because the claims have been amended.

Claim 67 filed on 03/08/2010 reads as follows: A pulse generator for generating electrical pulses comprising: a first circuit, the first circuit generating a first pulse having a duration of 700 nanoseconds up to and including 40 milliseconds and voltage amplitude of .1 kV/cm up to and including 5 kV/cm; a second circuit, the second circuit generating a second pulse having a duration of 700 picoseconds up to and including 1.3 milliseconds and voltage amplitude of 1 kV/cm up to and including 1000 kV/cm; and a control circuit for controlling the timing of said first circuit and said second circuit to respectively generate said first pulse and said second pulse.

Claims 68-77, 81-84, and 89-93 depend from claim 67.

2. Claims 67, 72-74, 81 and 89 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. *This rejection is necessitated by claim amendments filed on 03/08/2010.*

(I) Claim 67 recites the limitation “voltage amplitude of .1 kV/cm up to and including 5 kV/cm”. Claim 72 depends from claim 67 and recites the limitation “electric field strength of 0.1 kV/cm to 5 kV/cm”. It is unclear whether “.1 kV/cm” recited in claim 67 is meant to be “.1 kV/cm” or “1 kV/cm”. As a related issue, it is unclear whether “electric field strength” recited in claim 72 is the same as “voltage amplitude” recited in claim 67. Applicant is advised to clarify on the record regarding (i) the distinction, if any, between “electric field strength” recited in claim 72-74 and “voltage amplitude” recited in claim 67, and (ii) the distinction, if any, between the scope encompassed by claim 67 versus the scope encompassed by claim 72 regarding ranges of voltage amplitude/electric field strength.

(II) Claim 81 and 89 recite the limitation “said *high* voltage” in “a charging resistor coupled to said *high* voltage power supply”. There is insufficient antecedent basis for this limitation in the claim.

Claim Rejection - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

3. Previous rejection of claims 67-77 under 35 U.S.C. 102(b) as being anticipated by **Beebe et al.** (Beebe et al., Nanosecond pulsed electric field (nsPEF) effects on cells and tissues: apoptosis induction and tumor growth inhibition, *IEEE Transactions on Plasma Science*, 30 (1): 286-292, Feb. 2002; this reference is listed as reference CC in the IDS filed by Applicant on 10/18/2006) is **withdrawn** because the claims have been amended.

Claim 67 filed on 03/08/2010 reads as follows: A pulse generator for generating electrical pulses comprising: a first circuit, the first circuit generating a first pulse having a duration of 700 nanoseconds up to and including 40 milliseconds and voltage amplitude of .1 kV/cm up to and including 5 kV/cm; a second circuit, the second circuit generating a second pulse having a duration of 700 picoseconds up to and including 1.3 milliseconds and voltage amplitude of 1 kV/cm up to and including 1000 kV/cm; and a control circuit for controlling the timing of said first circuit and said second circuit to respectively generate said first pulse and said second pulse.

Claims 68-77 depend from claim 67.

Beebe et al. does not explicitly teach the limitation “the first circuit generating a first pulse having a duration of 700 nanoseconds up to and including 40 milliseconds and voltage amplitude of .1 kV/cm up to and including 5 kV/cm”.

4. Previous rejection of claims 67-72, 74-77, 81-84, and 89-93 under 35 U.S.C. 102(e) as being anticipated by **Gundersen et al.** (Gundersen et al., US 2003/0170898, publication date

09/11/2003, filed on 12/04/2002; this reference is listed as reference AD in the IDS filed by Applicant on 10/18/2006) is *withdrawn* because the claims have been amended.

Claim 67 filed on 03/08/2010 reads as follows: A pulse generator for generating electrical pulses comprising: a first circuit, the first circuit generating a first pulse having a duration of 700 nanoseconds up to and including 40 milliseconds and voltage amplitude of .1 kV/cm up to and including 5 kV/cm; a second circuit, the second circuit generating a second pulse having a duration of 700 picoseconds up to and including 1.3 milliseconds and voltage amplitude of 1 kV/cm up to and including 1000 kV/cm; and a control circuit for controlling the timing of said first circuit and said second circuit to respectively generate said first pulse and said second pulse.

Claims 68-77 depend from claim 67.

Gundersen et al. does not explicitly teach the limitation “a control circuit for controlling the timing of said first circuit and said second circuit to respectively generate said first pulse and said second pulse”.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

5. Claims 67-77, 81-84 and 89-93 are rejected under 35 U.S.C. 103(a) as being unpatentable over **Gundersen et al.** (Gundersen et al., US 2003/0170898, publication date 09/11/2003, filed on 12/04/2002; this reference is listed as reference AD in the IDS filed by Applicant on 10/18/2006) in view of **Yampolsky et al.** (US 2002/0140464, publication date 10/03/2002, filed

on 05/03/2001, which became US patent 6,831,377, issued on 12/14/2004). *This rejection is necessitated by claim amendments filed on 03/08/2010, which include claim amendments filed on 11/24/2009.*

Claim 67 filed on 03/08/2010 is directed to a pulse generator for generating electrical pulses comprising: a first circuit, the first circuit generating a first pulse having a duration of 700 nanoseconds up to and including 40 milliseconds and voltage amplitude of .1 kV/cm up to and including 5 kV/cm; a second circuit, the second circuit generating a second pulse having a duration of 700 picoseconds up to and including 1.3 milliseconds and voltage amplitude of 1 kV/cm up to and including 1000 kV/cm; and a control circuit for controlling the timing of said first circuit and said second circuit to respectively generate said first pulse and said second pulse [notes: 1000 picoseconds is 1 nanosecond, i.e. 10^{-9} second].

Claim 68 is directed to the pulse generator of claim 67, wherein said first pulse has a duration of 0.1 millisecond to 20 milliseconds.

Claim 69 is directed to the pulse generator of claim 67, wherein said first pulse has a duration of 0.001 millisecond to 30 milliseconds.

Claim 70 is directed to the pulse generator of claim 67, wherein said second pulse has a duration of 1 nanosecond to 300 nanoseconds.

Claim 71 is directed to the pulse generator of claim 67, wherein said second pulse has a duration of 1 nanosecond to 1000 nanoseconds [notes: 1000 nanoseconds is 1 microsecond, i.e. 10^{-6} second].

Claim 72 is directed to the pulse generator of claim 67, wherein said first pulse has an electric field strength of 0.1 kV/cm to 5 kV/cm.

Claim 73 is directed to the pulse generator of claim 67, wherein said first pulse has an electric field strength of 0.1 kV/cm to 1 kV/cm.

Claim 74 is directed to the pulse generator of claim 67, wherein said second pulse has an electric field strength of 10 kV/cm to 350 kV/cm.

Claim 75 is directed to the pulse generator of claim 67, wherein said second pulse has an electric field strength of 1 kV/cm to 1000 kV/cm.

Claim 76 is directed to the pulse generator of claim 67, wherein said control circuit allows an interval of 1 millisecond to 5 hours between said first pulse and said second pulse.

Claim 77 is directed to the pulse generator of claim 67, wherein said control circuit allows an interval of 1 millisecond to 24 hours between said first pulse and said second pulse.

Claim 81 is directed to the pulse generator of claim 67, wherein said first circuit comprises: a voltage power supply; a charging resistor coupled to said high voltage power supply; a capacitor coupled at a first end to said charging resistor and coupled at a second end to a load; and a transistor for controlling electrical discharge of said capacitor to the load.

Claim 82 is directed to the pulse generator of claim 81, wherein said transistor is responsive to at least one command from said control circuit to control the electrical discharge of said capacitor.

Claim 83 is directed to the pulse generator of claim 81, wherein said transistor has a low forward voltage for handling sustained high currents without suffering thermal damage.

Claim 84 is directed to the pulse generator of claim 81, wherein said transistor is an insulated gate bipolar transistor.

Claim 89 is directed to the pulse generator of claim 67, wherein said second circuit comprises: a voltage power supply; a charging resistor coupled to said high voltage power supply; and a transmission line coupled at a first end to said charging resistor and coupled at a second end to a load, said transmission line electrically discharging into the load.

Claim 90 is directed to the pulse generator of claim 89, wherein said transmission line is a Blumlein configuration transmission line.

Claim 91 is directed to the pulse generator of claim 89, further comprising a second switch coupled to and controlled by said control circuit, said second switch being operable to discharge the transmission line.

Claim 92 is directed to the pulse generator of claim 91, wherein said second switch is a spark gap switch.

Claim 93 is directed to the pulse generator of claim 91, further comprising a second trigger unit coupled to said control circuit for actuating said second switch responsive to a second command from said control circuit.

Claim interpretations: (i) The limitation “voltage amplitude of 1 kV/cm up to and including 5 kV/cm” recited in claim 67 is interpreted as “voltage amplitude of 0.1 kV/cm up to and including 5 kV/cm”. (ii) The limitations “a first circuit” and “a second circuit” recited in claim 67 are interpreted as two parallel and/or alternative routes in the flow of electricity within the circuits of claimed pulse generator designed to generate recited first pulse and second pulse with specified characteristics. (iii) The limitation “voltage amplitude” recited in claim 67 is interpreted as equivalent to the limitation “electric field strength” recited in claims 72-75.

With regard to claims 67, 70-72, 74, and 75, **Gundersen et al.** teaches methods with combined long and short pulse technology, and in one embodiment, a “long” electric field pulse is applied to cell followed by a “short” electric field pulse. Gundersen et al. teaches that long pulse lengths, such as pulses greater than 1 μsecond [which reads on the limitation 700 nanoseconds, i.e. 0.7 μ s, up to 40 milliseconds recited in claim 67] depending on the duration of electric field and on the desired membrane permeabilization, molecular uptake, or lysis from osmosis (See paragraphs [0003]-[0005], Gundersen et al., 2003/0170898). Gundersen et al. teaches that in one embodiment, the method includes applying at least one first electric field pulse to the cell sufficient to cause electroporation, incubating the cell with the therapeutic agent, and applying one or more second electric field pulses to one or more cells in the tissue, wherein each second electric field pulse has a pulse duration of less than about 100 nanoseconds [which reads on the limitations 700 picoseconds to 1.3 milliseconds of second circuit recited in claim 67, 1 nanosecond to 300 nanoseconds recited in claim 70, and 1 nanosecond to 1000 nanoseconds

recited in claim 71]. In a further embodiment, the pulse duration of the “short” pulse is less than about 1 nanosecond and the electric field is greater than about 10 kV/cm. In another embodiment, the pulse duration of the “long” pulse is greater than about 100 nanoseconds (See paragraph [0277], Gunderson et al., 2003/0170898). Gunderson et al. teaches that because the pulse characteristics require that the design of the pulse generator, matching of transmission line, and matching to the load (typically a cuvette with conductive solution containing cells with dielectric properties), must be engineered to match with these pulse shapes and pulse characteristics. In this regard, Gunderson et al. further teaches that a MOSFET-switched [which reads on a control circuit recited in claim 67, further elaborated by the teachings of Yampolsky et al. discussed below in this office action], inductive-adding pulse generator, using a balanced, coaxial-cable pulse-forming network and *spark-gap switch* for pulse shortening, was used. The pulse generators delivered electrical pulses to biological material in a variety of exposure modes, including, but not limited to, single-cell, detached-cell suspensions, and layers of cells in culture. The inductive adding pulse generator allowed application of the short pulses (typically about 5-10 kV) [which reads on the limitations 0.1 kV to 5kV/cm of first pulse and 1 kV to 1000 kV/cm of second pulse recited in claim 67; 0.1 kV to 5kV/cm of first pulse recited in claim 72; 10 kV/cm to 350 kV/cm of second pulse recited in claim 74; and 1 kV/cm to 1000 kV/cm of second pulse recited in claim 75], thereby providing large amplitude electric fields at the electrical load (e.g., within the cuvette) (See paragraph [0089], Gunderson et al., 2003/0170898, 2003).

With regard to the limitation “an electric field strength of 0.1 kV/cm to 1 kV/cm” recited in claim 73, Gunderson et al. teaches that long pulse lengths, such as pulses greater than 1 μ second depending on the duration of electric field and on the desired membrane

permeabilization, molecular uptake, or lysis from osmosis (See paragraphs [0003]-[0005], Gundersen et al., 2003/0170898). Accordingly, the recited electric strength in claim 73 is directed to optimization of ranges known in the art, see MPEP § 2131.03 cited below.

2144.05 [R-5] Obviousness of Ranges

See MPEP § 2131.03 for case law pertaining to rejections based on the anticipation of ranges under 35 U.S.C. 102 and 35 U.S.C. 102/103.

II. OPTIMIZATION OF RANGES

A. Optimization Within Prior Art Conditions or Through Routine Experimentation

Generally, differences in concentration or temperature will not support the patentability of subject matter encompassed by the prior art unless there is evidence indicating such concentration or temperature is critical. “[W]here the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.” *In re Aller*, 220 F.2d 454, 456, 105 USPQ 233, 235 (CCPA 1955) (Claimed process which was performed at a temperature between 40°C and 80°C and an acid concentration between 25% and 70% was held to be prima facie obvious over a reference process which differed from the claims only in that the reference process was performed at a temperature of 100°C and an acid concentration of 10%);

see also *Peterson*, 315 F.3d at 1330, 65 USPQ2d at 1382 (“The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of percentage ranges is the optimum combination of percentages.”); *In re Hoeschele*, 406 F.2d 1403, 160 USPQ 809 (CCPA 1969) (Claimed elastomeric polyurethanes which fell within the broad scope of the references were held to be unpatentable thereover because, among other reasons, there was no evidence of the criticality of the claimed ranges of molecular weight or molar proportions.). For more recent cases applying this principle, see *Merck & Co. Inc. v. Biocraft Laboratories Inc.*, 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), cert. denied, 493 U.S. 975 (1989); *In re Kulling*, 897 F.2d 1147, 14 USPQ2d 1056 (Fed. Cir. 1990); and *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997).

B. Only Result-Effective Variables Can Be Optimized

A particular parameter must first be recognized as a result-effective variable, i.e., a variable which achieves a recognized result, before the determination of the optimum or workable ranges of said variable might be characterized as routine experimentation. In re Antonie, 559 F.2d 618, 195 USPQ 6 (CCPA 1977) (The claimed wastewater treatment device had a tank volume to contractor area of 0.12 gal./sq. ft. The prior art did not recognize that treatment capacity is a function of the tank volume to contractor ratio, and therefore the parameter optimized was not recognized in the art to be a result-effective variable.). See also In re Boesch, 617 F.2d 272, 205 USPQ 215 (CCPA 1980) (prior art suggested proportional balancing to achieve desired results in the formation of an alloy).

With regard to the limitation "first pulse has a duration of 0.1 millisecond to 20 milliseconds" recited in claim 68 and the limitation "first pulse has a duration of 0.001 millisecond to 30 milliseconds" recited in claim 69, Gundersen et al. teaches that in a further embodiment, the pulse duration of the relatively "long" pulse is greater than about 100 nanoseconds. In another embodiment, the pulse duration of the relatively "long" pulse is greater than about 1 millisecond (See paragraph [0017], Gundersen et al., 2003/0170898, 2003).

With regard to the intervals between said first pulse and said second pulse recited in claim 76 [1 millisecond to 5 hours] and claim 77 [1 millisecond to 24 hours], Gundersen et al. teaches that dose-response and time course of Jurkat cells in response to the UPSET pulse treatment: 20 to 50 repetitive UPSET shocks of 20 kV/cm, 20 nanoseconds with a 3 nanosecond rise time at 20 Hz caused significant apoptosis and gene expression changes in Jurkat cells. Gundersen et al. teaches that to characterize the dose-response of the Jurkat cells to the UPSET shocks, parameters were changed sequentially one parameter at a time. The field strength in the range of 10 kV/cm to 300 kV/cm, the pulse width in the range of 0.1 nanosecond to 100

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nanoseconds, and the pulse frequency in the range of 1 hz to 10 khz were tested. The pulse pattern and the rising time of the pulses were also examined (See paragraph [0247], Gundersen et al., 2003/0170898, 2003). Gundersen et al. teaches that one skilled in the art will also understand that studies can also be performed at time intervals other than post 1 hour and post 6 hours after treatment (See paragraph [0116], Gundersen et al., 2003/0170898, 2003).

With regard to the limitations of the first circuit and the second circuit recited in claims 81, 89, and 91, Gundersen et al. teaches that the load behaves as a parallel combination of a *resistor* and a *capacitor*, with an RC time constant, $\tau_L = \rho \epsilon_0$, of approximately 3 nanoseconds. This is comparable to the pulse length. The pulse generator was designed to see a load impedance of $Z_L \sim 20 \Omega$ (See paragraph [0134], Gundersen et al., 2003/0170898, 2003). Gundersen et al. teaches a MOSFET-switched, inductive-adding pulse generator, using a balanced, coaxial-cable pulse-forming network and *spark-gap switch* [which reads on the limitation recited in claim 91 of instant application] for pulse shortening, was used (See Figures 21 of Gundersen et al., 2003, which is also provided below in this office action].

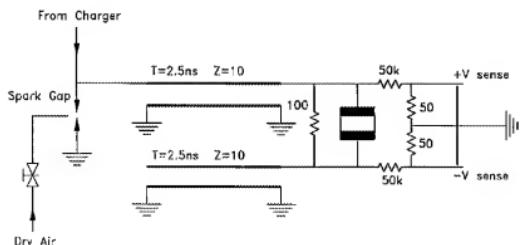


FIG. 21

Gundersen et al. teaches that the pulse generators delivered electrical pulses to biological material in a variety of exposure modes, including, but not limited to, single-cell, detached-cell suspensions, and layers of cells in culture. The inductive adding pulse generator allowed application of the short pulses (typically about 5-10 kV and about 20 nanoseconds), thereby providing large amplitude electric fields at the electrical load (e.g., within the cuvette). (See paragraphs [0089], Gundersen et al., US 2003/0170898, 2003). It is noted that the MOSFET-switched, inductive-adding pulse generator encompasses MOSFET transistors for determination of conductivity [See the middle of the diagram labeled APT10035JFLL in Figure 23 of Gundersen et al., 2003 provided below in this office action].

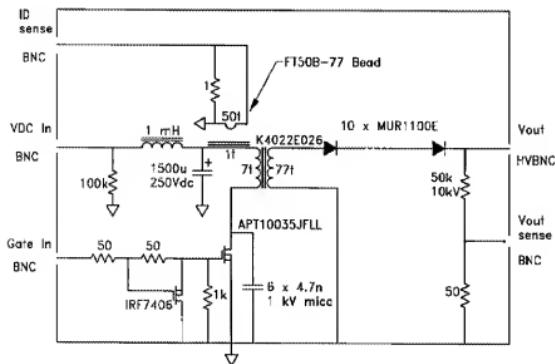


FIG. 23

Therefore, the MOSFET-switched, inductive-adding pulse generator reads on transistor for controlling electrical discharge of said capacitor to the load recited in claims 81 and 89 of instant application. This interpretation of MOSFET-switched, inductive-adding pulse generator and Figure 23 disclosed by Gubdersen et al. are further supported by the disclosures in paragraph

[0042] regarding a well-formed 50 kV pulse using small voltage switches (e.g. MOSFET transistors), and the disclosures in paragraph [0049] regarding APT5010LVR transistor, by **Yampolsky et al.**, US 2002/0140464, publication date 10/03/2002.

With regard to the limitations recited in claims 82-84 and 91-93 regarding characteristics of transistor in the context of controlling electrical discharge, Gundersen et al., in addition to the disclosures of Figures 21 and 23 [which reads on the limitation of claim 82] discussed above in this rejection, teaches that in one embodiment, the gate driver is the matching DEIC420 chip incorporating the same low inductance design as the MOSFET. The fast switching speed of the MOSFET gate causes large oscillations in the drive circuit [which reads on the limitation insulated gate bipolar transistor recited in claim 84 of instant application]. Switching noise is sufficiently large to cause false triggering of the MOSFET after short pulses <60 nanoseconds. The gate pin noise with no filtering is 18.6 Vpeak having an oscillation frequency of 36 MHz. The gate drive IC propagates the noise through even to its logic level input pin. The DEIC420 driver VCC power pin is 15 V and shows 500 mV peak noise spike with or without gate filtering. Thus, power supply noise is not responsible for the large swings on the gate drive signal. The gate noise is also independent of MOSFET load and drain voltage (See paragraph [0176], **Gundersen et al.**, US 2003/0170898, 2003). Gundersen et al. further teaches that saturable reactor filtering is placed in series with the gate driver and gate to reduce *switching spikes* at the gate. Drain fall time is slowed from 3.1 nanoseconds to 3.8 nanoseconds by the addition of gate filtering for 16.2 Vpeak noise and partial false triggering of the MOSEFET after turn-off from a 20 nanoseconds pulse. Sufficient inductance reducing the drain fall time to 4.2 nanoseconds results in 13.2 V peak noise on the gate and no false triggering of the MOSFET [which reads on

the limitation handling sustained high currents without suffering thermal damage recited in claim 83 of instant application]. The chosen filter inductor includes a copper wire and two saturable reactors in parallel. Both of the saturable reactors are Toshiba Spike Killer SA7 x 6 x 4.5 magnetic cores with one turn each. Fig. 10 shows the cost in drain fall time to achieve noise suppression using varying combinations of paralleled conductors and saturable reactors. At 13.2 V and below, the MOSFET experiences no false triggering after a 20 nanosecond pulse (See paragraph [0177], Gundersen et al., US 2003/0170898, 2003).

With regard to the limitations recited in claims 90-93 regarding the configuration of second circuit, Gundersen et al., in addition to the disclosures of Figures 21 and 23 discussed above in this rejection, teaches that the *Blumlein configuration* (See Figure 21, Gundersen et al., 2003, shown above in this rejection) includes two identical series connected *transmission lines* charged to a common voltage. Each individual line has a characteristic impedance half that of the load (See paragraph [0134], Gundersen et al., 2003/0170898, 2003). Gundersen et al. teaches that the maximum allowable charge time defines a maximum inductance, L_S , in series with the transmission line. The charging waveform is approximately one quarter of the period of the resonant circuit formed by this inductance and the load capacitance. This limits the inductance of the secondary winding of the high-voltage transformer (See paragraph [0153], Gundersen et al., 2003/0170898, 2003).

Gundersen et al. does not explicitly teach the “MOSFET-switched” inductive-adding pulse generator which comprises “a control circuit for controlling the timing of said first circuit and said second circuit to respectively generate said first pulse and said second pulse” as recited in claim 67.

At the time of filing of instant application, a “MOSFET-switched” inductive-adding pulse generator comprising “a control circuit for controlling the timing of said first circuit and said second circuit to respectively generate said first pulse and said second pulse” is known in the art. For instance, **Yampolsky et al.** teaches solid-state pulse generator using a split magnetic core transformer is described. In one embodiment, the solid-state drive circuit uses MOSFETs switching a *blumlein* [which, as the teachings of Gubdersen et al. discussed above, reads on the limitation of claim 90] to produce a desired input pulses in a primary winding of the split magnetic core. The pulse length is determined primarily by the characteristics of the blumlein and the split core transformer. The “on” time of the solid-state devices can exceed the output pulse length, thereby reducing the chance of damaging voltage spikes. *The use of a split magnetic core allows several solid-state drive circuits to be used in parallel to produce a single output pulse* [which reads on the limitation “a control circuit for controlling the timing of said first circuit and said second circuit to respectively generate said first pulse and said second pulse” recited in claim 67]. In one embodiment, each solid-state drive circuit drives a separate single-turn primary winding of a split magnetic core transformer. In one embodiment, each core of the split core transformer has one primary winding. The separate cores of the split core transformer are provided with a single secondary winding that couples all of the cores to produce a relatively high-voltage output pulse with relatively few turns in the secondary winding (See abstract, Yampolsky et al., US 2002/0140464).

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time of the invention to incorporate the teachings of Yampolsky et al. (2002) regarding the use of a split magnetic core allows several solid-state drive circuits to be used in parallel to

produce a single output pulse in a MOSFET-switched inductive-adding pulse generator, into the teachings of Gunderson et al. (2003) regarding the method includes applying at least one *first electric field pulse*, with pulse duration of the relatively "long" pulse is greater than about 1 millisecond, to the cell sufficient to cause electroporation, incubating the cell with the therapeutic agent, and applying one or more *second electric field pulses* to one or more cells in the tissue, wherein each second electric field pulse has a pulse duration of less than about 100 nanoseconds, in a MOSFET-switched inductive-adding pulse generator, to arrive at the pulse generator recited in claims 67-77, 81-84 and 89-93 of instant application.

One having ordinary skill in the art would have been motivated to incorporate the incorporate the teachings of Yampolsky et al. (2002) into the teachings of Gunderson et al. (2003) because Yampolsky et al. (2002) provides specific teachings on how the split magnetic core of MOSFET-switched inductive-adding pulse generator, which is the pulse generator taught by Gunderson et al. (2003), control the timing of said first circuit and said second circuit to respectively generate said first pulse and said second pulse.

There would have been a reasonable expectation of success given (i) disclosure of the method includes applying at least one *first electric field pulse*, with pulse duration of the relatively "long" pulse is greater than about 1 millisecond, to the cell sufficient to cause electroporation, incubating the cell with the therapeutic agent, and applying one or more *second electric field pulses* to one or more cells in the tissue, wherein each second electric field pulse has a pulse duration of less than about 100 nanoseconds, in a MOSFET-switched inductive-adding pulse generator, by the teachings Gunderson et al., and (iii) disclosure of the use of a split magnetic core allows several solid-state drive circuits to be used in parallel to produce a output

pulse with desired duration and amplitude in a MOSFET-switched inductive-adding pulse generator, by the teachings Yampolsky et al.

Thus, the claimed invention as a whole was clearly *prima facie* obvious

Applicant's remarks filed on 03/08/2010 regarding the previous 102 rejections of record are addressed as the related to the new grounds of 103 rejection set forth above.

The Examiner would like to direct Applicant's attention to recent decision by U.S. Supreme Court in *KSR International Co. v. Teleflex, Inc.* that forecloses the argument that a **specific** teaching, suggestion, or motivation is an absolute requirement to support a finding of obviousness. See recent Board decision *Ex parte Smith*, --USPQ2d--, slip op. at 20, (Bd. Pat. App. & Interf. June 25, 2007) (citing KSR, 82 USPQ2d at 1936) (available at <http://www.uspto.gov/web/offices/dcom/bpai/prec/fd071925.pdf>). The Examiner notes that in the instant case, even in the absence of recent decision by U.S. Supreme Court in *KSR International Co. v. Teleflex, Inc.*, the suggestion and motivation to combine Lange et al., Schulein et al., and Dunn-Coleman et al. has been clearly set forth above in this office action.

It is noted that one cannot show nonobviousness by attacking references individually where the rejections are based on combinations of references. See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986).

The following statements are relevant to the claimed product (a pulse generator) even though the claims are not written as product-by-process claims.

Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the

characteristics of his claimed product (*In re Ludtke*). Whether the rejection is based on “inherency” under 35 USC 102, on “*prima facie* obviousness” under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced by the PTO’s inability to manufacture products or to obtain and compare prior art products. *In re Best, Bolton, and Shaw*, 195 USPQ 430, 433 (CCPA 1977) citing *In re Brown*, 59 CCPA 1036, 459 F.2d 531, 173 USPQ 685 (1972)).

“When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not.” *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). Therefore, the *prima facie* case can be rebutted by evidence showing that the prior art products do not necessarily possess the characteristics of the claimed product. *In re Best*, 562 F.2d at 1255, 195 USPQ at 433. See also *Titanium Metals Corp. v. Banner*, 778 F.2d 775, 227 USPQ 773 (Fed. Cir. 1985), *In re Ludtke*, 441 F.2d 660, 169 USPQ 563 (CCPA 1971), *Northam Warren Corp. v. D. F. Newfield Co.*, 7 F. Supp. 773, 22 USPQ 313 (E.D.N.Y. 1934.) See MPEP 2113 and MPEP 2112.01.

[E]ven though product-by-process claims are limited by and defined by the process, determination of patentability is based on the product itself. The patentability of a product does not depend on its method of production. If the product in the product-by-process claim is the same as or obvious from a product of the prior art, the claim is unpatentable even though the prior product was made by a different process.” *In re Thorpe*, 777 F.2d 695, 698, 227 USPQ 964, 966 (Fed. Cir. 1985).

“The Patent Office bears a lesser burden of proof in making out a case of *prima facie* obviousness for product-by-process claims because of their peculiar nature” than when a product is claimed in the conventional fashion. *In re Fessmann*, 489 F.2d 742, 744, 180 USPQ 324, 326 (CCPA 1974). Once the examiner provides a rationale tending to show that the claimed product appears to be the same or similar to that of the prior art, although produced by a different process, the burden shifts to applicant to come forward with evidence establishing an unobvious difference between the claimed product and the prior art product. *In re Marosi*, 710 F.2d 798, 802, 218 USPQ 289, 292 (Fed. Cir. 1983).

Conclusion

6. No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Any inquiry concerning this communication from the examiner should be directed to Wu-Cheng Winston Shen whose telephone number is (571) 272-3157 and Fax number is 571-273-3157. The examiner can normally be reached on Monday through Friday from 8:00 AM to 4:30 PM. If attempts to reach the examiner by telephone are unsuccessful, the supervisory patent

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examiner, Peter Paras, Jr. can be reached on (571) 272-4517. The fax number for TC 1600 is (571) 273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Wu-Cheng Winston Shen/

Primary Examiner

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